European Heart Journal (2002) **23,** 550–557
doi:10.1053/euhj.2001.2901, available online at http://www.idealibrary.com on IDEAL®

Clinical characteristics and outcome of patients with early (<2 h), intermediate (2–4 h) and late (>4 h) presentation treated by primary coronary angioplasty or thrombolytic therapy for acute myocardial infarction

F. Zijlstra, A. Patel, M. Jones, C. L. Grines, S. Ellis, E. Garcia, L. Grinfeld, R. J. Gibbons, E. E. Ribeiro, F. Ribichini, C. Granger, F. Akhras, W. D. Weaver and R. J. Simes for the PCAT collaboration

Department of Cardiology, Hospital De Weezenlanden, Zwolle, The Netherlands

Aims We examined the clinical characteristics and outcome of patients with early (<2 h), intermediate (2–4 h) and late (>4 h) presentation treated by primary angioplasty or thrombolytic therapy for acute myocardial infarction.

Methods and Results We studied 2635 patients enrolled in 10 randomized trials of primary angioplasty (n=1302) vs thrombolytic therapy (n=1333) in acute myocardial infarction, and baseline characteristics of the two groups were comparable. Increase in presentation delay is associated with older age, female gender, diabetes and an increased heart rate. We classified the patients according to the time delay from symptom onset to presentation into three categories: early presentation (<2 h), intermediate presentation (2–4 h), and late presentation (≥4 h). At 30 days the combined rate of death, non-fatal reinfarction and stroke in patients presenting early was 5·8% in the angioplasty group vs 12·5% in the thrombolysis group, in patients with intermediate presentation, 8·6% vs 14·2%, respectively, and in patients presenting late 7·7% vs 19·4%, respectively. With increasing time from symptom onset to presentation, all major adverse cardiac event rates show a trend to a larger increase in the thrombolysis group compared to the angioplasty group, both at 30 days and at 6 months after the acute event.

Conclusions Major adverse cardiac event rates are lower after angioplasty compared to thrombolysis, irrespective of time to presentation. With increasing time to presentation major adverse cardiac event rates increase after thrombolysis but appear to remain relatively stable after angioplasty.
(Eur Heart J 2002; 23: 550–557, doi:10.1053/euhj.2001.2901)

Key Words: Myocardial infarction, thrombolytic therapy, coronary angioplasty.

Introduction

It has been shown convincingly that several modes of reperfusion therapy for acute myocardial infarction started within 6 h (or 12 h) after symptom onset result in an important mortality reduction[1,2], but there is no certainty about the relationship between ischaemic time and clinical outcome. There is clear evidence that early treatment, especially within the first 'golden hour' results in a considerable mortality benefit[1–3]. Studies that have addressed the influence of time to treatment, including patients who present relatively late after the onset of symptoms, suggest that there may be clinically important differences in the time-dependent efficacy of various reperfusion therapies[4–8]. Most studies report on patients treated with thrombolytic therapy. It is not known whether reperfusion actually occurs in these patients, and if so, the time is uncertain. In patients undergoing primary angioplasty, more information is available concerning the moment of reperfusion of the

Revision submitted 10 July 2001, accepted 11 July 2001, and published online 4 October 2001.

Correspondence: Dr Felix Zijlstra, Hospital de Weezenlanden, Department of Cardiology, Groot Wezenland 20, 8011 JW Zwolle, The Netherlands.

0195-668X/02/070550+08 $35.00/0

epicardial coronary artery. However, in comparative studies of angioplasty vs thrombolytic therapy the only time frames that can be compared is symptom onset to hospital admission or to randomization. The time from hospital admission or randomization to start of therapy introduces an important confounding variable as this time is an indirect marker of both the type and quality of care and therefore can influence outcome by itself.

A clear relationship between time from hospital admission to outcome after treatment with primary angioplasty has been described, although in the same cohorts of patients no relationship was found between time from symptom onset to treatment and clinical outcome[9,10]. Several clinical variables (age, female gender, diabetes) are strongly related to time from symptom onset to presentation. The influence of age on clinical outcome is also very strong[11]. In the GUSTO 1 trial, age, haemodynamic variables and infarct location contained 90% of the prognostic information of the baseline clinical data to predict 30-day mortality in patients treated with thrombolytic therapy for acute myocardial infarction[12]. Therefore, we compared patient characteristics and outcome in a large cohort of patients according to time intervals between onset of symptoms and presentation (hospital admission or randomization). Patients were treated with primary coronary angioplasty or thrombolytic therapy. In thrombolysis patients, we investigated whether there is a difference in time-dependence between rtPA and streptokinase.

Methods

Research questions and eligibility criteria

We sought to study data from randomized comparisons of patients treated with intravenous thrombolytic drug therapy and primary PTCA. We attempted to identify all published and unpublished randomized trials that compared intravenous thrombolytic drug therapy with primary PTCA. The trial search strategy and process has been described[2]. Primary analysis was based on mortality, non-fatal reinfarction and stroke at 30 days, and mortality and non-fatal reinfarction up to 6 months. The analysis examined the effects of presentation delay on outcomes after primary PTCA and intravenous thrombolytic therapy. With one exception, individual data from all randomized trials comparing PTCA vs intravenous thrombolysis in patients with acute myocardial infarction commencing prior to 31 December 1995 were included. One additional trial was identified subsequent to the previous meta-analysis[2,13–23]. We were unable to obtain individual data for one study[23]. Eligible trials were not confounded on other major treatments such as heparin and aspirin. In one trial, hirudin was given to almost half of each of the two randomized groups. Definition of eligible patients was according to each protocol but for most trials was confined to patients with suspected acute myocardial infarction having ST elevation of at least 1 mm in two contiguous leads or suspected new left bundle branch block. No major contraindications for the use of thrombolytic drug therapy, and randomization within 12 h of suspected acute coronary occlusion, was required.

Quality review

Systematic quality review of each trial was conducted to determine whether each trial was truly randomized, that there were no exclusions from analysis, the extent to which outcome adjudication was blinded, and the exact period of follow-up. Any discrepancies between the individual data and previously published results were queried and resolved by the investigator. Source document verification of the data was not routinely performed.

Definitions of time to presentation and outcomes

Time to presentation was measured from the onset of symptoms to randomization in six trials and from symptom onset to hospital admission in three trials and was unavailable in one trial. The same definition was used for thrombolytic and angioplasty treated patients within each trial. Outcomes for comparison were total mortality, non-fatal reinfarction, death or non-fatal reinfarction and total stroke. Outcome definitions used by each individual trial were used. Outcomes at 30 days and 6 months were sought for all patients.

Subgroup analyses

A number of subgroups were investigated to allow multivariate analysis. Subgroups examined were defined by the lytic regimen used, age (<50, 50–60, 60–70, and >70 years), gender, diabetes, infarct location, history of prior myocardial infarction, heart rate on admission (<65, 65–75, 75–85, and >85 beats . min^{-1}) and systolic blood pressure on admission (<115, 115–130, 130–150 and >150 mmHg). Age, heart rate and systolic blood pressure cut-offs represent approximate quartiles.

Statistical methods

All comparisons were based on an intention-to-treat analysis according to randomized groups. Logistic regression, adjusted by individual trial, was used to calculate odds ratios, 95% confidence intervals, *P*-values as well as to calculate *P*-values for tests for trend. No adjustment was made for multiple comparisons. Tests for heterogeneity of treatment effect across trials and other variables was assessed using a test for interaction or trend within the logistic regression analysis[24].

Results

The findings of this study are based on 10 randomized trials with individual patient data[13–22], and include a

Table 1 Summary of trials

Study	Primary coronary angioplasty		Thrombolytic therapy	
	No. patients	Stents (%)	No. patients	Agent
Zijlstra *et al.*[13]	152	—	149	$1{\cdot}5 \times 10^6$ U, Sk, 1 h
Ribeiro *et al.*[14]	50	—	50	$1{\cdot}2 \times 10^6$ U, Sk, 1 h
Grinfeld *et al.*[15]	54	—	58	$1{\cdot}5 \times 10^6$ U, Sk, 1 h
Zijlstra *et al.*[16]	47	—	53	$1{\cdot}5 \times 10^6$ U, Sk, 1 h
Garcia *et al.*[17]	95	13	94	tPA, 90 min
Grines *et al.*[18]	195	—	200	tPA, 3 h
Gibbons *et al.*[19]	47	—	56	Duteplase, 4 h
GUSTO 2B[20]	565	5	573	tPA, 90 min
Akhras *et al.*[21]	42	—	45	$1{\cdot}5 \times 10^6$ U, Sk, 1 h
Ribichini *et al.*[22]	55	58	55	tPA, 90 min

Sk = streptokinase; tPA = tissue plasminogen activator.

total of 2635 patients, 1302 allocated to primary angioplasty, and 1333 allocated to intravenous thrombolytic therapy. Thrombolytic therapy was streptokinase in five trials (355 patients), tissue plasminogen activator (tPA) regimens given over 3–4 h in three trials (300 patients) and tPA given over 90 min in three trials (722 patients). A summary of the trials is given in Table 1. Time from symptom onset to presentation was recorded in 1224/1302 (94%) patients in the angioplasty group and in 1262/1333 (95%) patients in the thrombolysis group. In the angioplasty group, 414 patients (32%) presented early (<2 h), 512 patients (39%) intermediate (2–4 h) and 297 patients (23%) late (>4 h) after symptom onset, comparable to 424 (32%), 523 (39%) and 315 (24%), respectively, in patients in the thrombolysis group. The median time from randomization to treatment was recorded in 1222/1302 (94%) patients in the angioplasty group, median 69 min, 25%–75% percentiles 51/90 min. The median time from randomization to start of thrombolytic therapy was recorded in 1193/1333 (89%) patients in the thrombolysis group, median 22 min, 25%–75% percentiles 14/35 min. Time from symptom onset to presentation had no influence on the delay from presentation to start of therapy, in either angioplasty or thrombolysis patients.

The clinical characteristics of the patients are shown in Table 2. Presentation delay is associated with older age, female gender, diabetes and an increased heart rate. The clinical characteristics of angioplasty and thrombolysis patients are comparable. Major adverse event rates are shown in Table 3 and Fig. 1 (30 days), and Table 4 and Fig. 2 (6 months). All major adverse event rates are lower in angioplasty patients compared to thrombolysis patients. With increasing time from symptom onset to presentation, major adverse event rates were observed to increase in the thrombolysis patients ($P<0{\cdot}04$) but not in the angioplasty patients ($P>0{\cdot}4$). However, the trend to a greater increase in the thrombolysis group compared with the angioplasty group was not statistically significant ($P \geq 0{\cdot}06$). Univariate and multivariate analysis of risk factors for mortality at 30 days is shown in Table 5. Time from symptom onset was significant in univariate analysis, but no longer significant after adjustment for the other important parameters. Multivariate analysis performed separately for angioplasty and thrombolysis patients is shown in Table 6. In Table 7, mortality at 30 days and 6 months is shown according to thrombolytic agent. Both streptokinase and rtPA showed a similar pattern of increasing mortality with increasing time to presentation.

Discussion

The major findings of this analysis are that irrespective of the time to presentation, patients allocated to primary angioplasty have a lower rate of major adverse events compared to patients allocated to thrombolytic therapy, both at 30 days and at 6 months. There is a significant increase in the major adverse event rate in thrombolysis patients, with increasing time to presentation, whereas in angioplasty patients the rate of major adverse events seems comparatively stable. Furthermore, our data confirm that time to presentation is strongly related to several important determinants of outcome, in particular age, gender, infarct location and haemodynamic status. In a multivariate model, after adjustment for these variables, time to treatment was no longer significantly associated with outcome. Time from symptom onset to presentation was measured differently in the nine trials where data were available: in six trials time to randomization was used while in three trials time to hospital admission was recorded. In all cases the same definition was used within each trial so that no bias in comparisons between the two treatment groups have been introduced.

Time dependence of outcome after thrombolytic therapy

The duration of coronary occlusion and the extent of collateral circulation are the main determinants of myocardial infarct size in various animal models[25–27].

Table 2 Clinical characteristics

	Primary coronary angioplasty				Thrombolytic therapy			
	Early (n=414)	Intermediate (n=512)	Late (n=297)	Trend analysis *P*	Early (n=424)	Intermediate (n=523)	Late (n=315)	Trend analysis *P*
Presentation time (min) (25%–75%)	82 (60, 100)	161 (135, 187)	335 (270, 475)		80 (60, 100)	163 (139, 190)	337 (275, 465)	
Age (years)	60 (51, 68)	62 (54, 70)	65 (55, 72)	0·0001	59 (50, 68)	62 (53, 70)	64 (55, 72)	0·0001
Male gender	84·1%	73·4%	73·4%	0·001	81·6%	76·1%	74·9%	0·024
Previous PTCA	4·2%	4·9%	2·6%	0·37	4·8%	5·2%	4·2%	0·74
Diabetes	9·6%	15·9%	25%	0·001	8·9%	13·4%	20·1%	0·001
Previous CABG	1%	2·4%	2·6%	0·12	2·7%	4·4%	3·5%	0·47
Heart rate (beats . min^{-1})	70 (60, 84)	74 (62, 85)	79 (65, 90)	0·0001	70 (60, 82)	73 (62, 85)	78 (67, 90)	0·0001
Systolic blood pressure	130 (115, 147)	130 (115, 150)	130 (115, 150)	0·14	130 (110, 145)	130 (115, 145)	130 (118, 150)	0·07
Previous MI	13%	15%	14·8%	0·47	16·5%	14·9%	11·8%	0·075
Anterior MI	47·8%	40·6%	44·8%	0·31	44·8%	41·4%	45·4%	0·97

Presentation time=time from symptom onset to presentation (early <2 h; intermediate 2–4 h; late ≥4 h); MI=myocardial infarction; CABG=coronary artery bypass surgery; PTCA=percutaneous transluminal coronary angioplasty; CAD=coronary artery disease.

Table 3 Death, reinfarction and stroke at 30 days follow-up

	Primary coronary angioplasty				Thrombolytic therapy				
	Early (n=414)	Intermediate (n=512)	Late (n=297)	*P*-value for trend	Early (n=424)	Intermediate (n=523)	Late (n=315)	*P*-value for trend	Test for interaction*
Death (%)	3·9	4·1	4·7	0·9	5·0	6·3	12·1	0·0005	0·16
Death and non-fatal reinfarction	5·6	8·2	7·1	0·5	11·6	12·6	18·1	0·02	0·09
Death, non-fatal reinfarction and stroke	5·8	8·6	7·7	0·4	12·5	14·2	19·4	0·01	0·09

*The test for interaction compares whether the trend in event rates according to presentation time differs significantly between the angioplasty and thrombolysis groups.

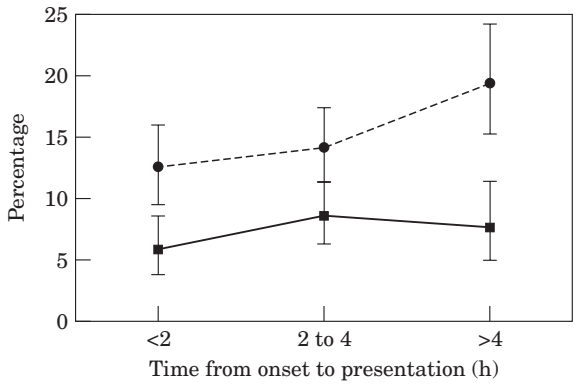

***Figure 1* Time dependency of primary PTCA vs thrombolysis. Rate of death, non-fatal reinfarction and stroke at 30 days (with 95% confidence intervals) in patients presenting early (<2 h), intermediate (2–4 h) and late (≥4 h). ● = the percentage of thrombolysis patients who died, suffered non-fatal reinfarction and stroke at 30 days; ■ = the percentage of primary PTCA patients who died, suffered non-fatal reinfarction and stroke at 30 days.**

Occlusions persisting for ≤30 min generally do not lead to significant damage. At ±90 min the extent of cell death involves 40%–50% of myocardium at risk, and after 6 h of continuous ischaemia, myocardial salvage will be minimal, unless collateral flow is very good[25–27]. There is a continuing debate as to whether this relationship between time delay and outcome following thrombolytic therapy is linear[1] or non-linear, with a significant additional benefit for very early treatment[3]. Myocardial infarct size measurements suggest that with respect to myocardial salvage, there may indeed be a 'golden hour' of reperfusion[11,28–30]. It has been suggested by angiographic studies[5,6] that the time dependent decrease in efficacy of thrombolytic therapy may differ between thrombolytic regimens, with front-loaded rtPA being less time dependent than streptokinase. The ALKK-study group described a TIMI 3 patency of 37% in patients treated within 3 h (n=133) and 28% in patients treated after 3 h (n=76) with streptokinase, compared to 73% (n=190) and 76% (n=86) after front-loaded rtPA[6]. Steg and co-workers[5] showed a decrease in efficacy of streptokinase after a 6-h time delay, in a small group of patients (n=13). In our larger groups of patients there was no significant difference in the pattern of 30-day or 6 month outcomes between streptokinase and tPA, according to time from presentation. In both cases clinical outcome was worse with longer time delay, in contrast to the pattern observed following primary angioplasty. However, it seems likely that a much larger study population would be necessary to establish subtle differences in clinical outcome after various thrombolytic regimens[31]. In the GUSTO-1 trial, longer presentation and treatment delays were both associated with increased mortality, but had no influence on the relative benefits of streptokinase compared to accelerated t-PA[32].

Time independence of outcome after primary angioplasty?

Our data are consistent with previous observations[4,7,8] that the relationship between time delay and outcome

Table 4 Death, reinfarction at 6 months follow-up

	Primary coronary angioplasty				Thrombolytic therapy				
	Early (n=414)	Intermediate (n=512)	Late (n=297)	*P*-value for trend	Early (n=424)	Intermediate (n=523)	Late (n=315)	*P*-value for trend	Test for interaction*
Death (%)	5·1	6·1	6·7	0·6	5·4	7·3	14·6	0·0001	0·10
Death and non-fatal reinfarction	8·2	11·7	9·8	0·6	15·1	14·9	21·6	0·04	0·06

*The test for interaction compares whether the trend in event rates according to presentation time differs significantly between the angioplasty and thrombolysis groups.

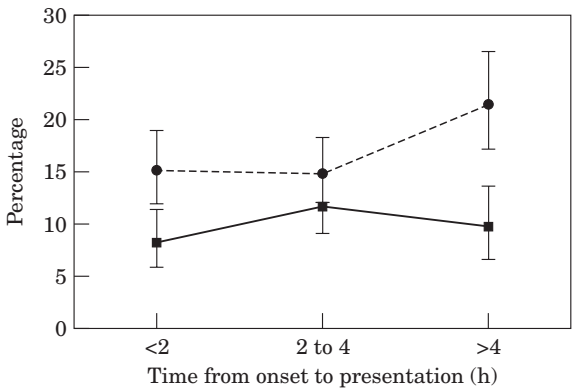

Figure 2 **Time dependency of primary PTCA vs thrombolysis. Rate of death, and non-fatal reinfarction at 6 months (with 95% confidence intervals) in patients presenting early (<2 h), intermediate (2–4 h) and late (≥4 h). ● = the percentage of thrombolysis patients who died and suffered non-fatal reinfarction at 6 months; ■ = the percentage of primary PTCA patients who died, suffered non-fatal reinfarction and stroke at 6 months.**

Table 5 Univariate and multivariate analysis of risk factors for 30 day mortality in 2635 patients treated with primary angioplasty or thrombolytic therapy

	Univariate analysis		Multivariate analysis	
	Odds ratio	*P*-value	Odds ratio	*P*-value
Age				
<50 years	1·0	0·0001	1·0	<0·0001
50–60 years	2·2		2·2	
60–70 years	3·9		4·3	
>70 years	14·1		15·1	
Heart rate				
<65 min	1·0	0·03	1·0	0·02
65–74 min	0·94		1·1	
75–84 min	0·89		1·2	
≥85 min	1·7		2·0	
Time to presentation				
<2 h	1·0	0·007		ns
2–4 h	1·2			
4–6 h	1·7			
≥6 h	2·4			
Diabetes	1·9	0·003		ns
Female gender	2·4	0·0001		ns
Anterior infarction	1·6	0·01	1·6	0·02
Previous infarction	1·5	0·04	1·6	0·04
SBP (mmHg)				
≥150	1·0	0·0002	1·0	<0·0001
130–149	0·96		1·2	
115–129	1·0		1·5	
<115	2·3		3·0	
Primary angioplasty	0·59	0·003	0·62	0·01

may differ in patients treated with primary angioplasty compared to thrombolytic therapy.

However, since tests for interaction between time dependence of outcome for each treatment were not statistically significant, this could also be a chance finding. One potential explanation for real interactions

Table 6 Multivariate analysis of risk factors for 30 day mortality in 1302 patients allocated to primary angioplasty, compared to 1333 patients allocated to intravenous thrombolytic therapy

	Primary angioplasty		Thrombolytic therapy	
	Odds ratio	*P*-value	Odds ratio	*P*-value
Age				
<50 years	1·0	0·002	1·0	0·0001
50–60 years	2·4		1·9	
60–70 years	4·6		3·4	
>70 years	9·2		18·7	
SBP				
≥150	1·0	0·03	1·0	0·005
130–149	1·3		1·0	
115–129	1·4		1·4	
<115	3·0		2·8	
Anterior MI		ns	1·9	0·02
Prior MI		ns	1·8	0·05

with treatment is that short-term outcome is mainly determined by flow in the epicardial infarct related coronary artery. Angioplasty is effective in restoring flow in a large majority of patients with acute myocardial infarction regardless of time to presentation. Patients treated early may do somewhat better[7,8]. However, our data suggest that this is mainly due to clinical characteristics of these patients. Although time in general seems to play only a modest role in the clinical outcome after reperfusion therapy, it is important to realize that patients who actually undergo effective reperfusion therapy in the first 1 or 2 h after the onset of symptoms are an exception. Both after treatment with thrombolysis[29,30] as well as angioplasty[7,28], patients treated within 2 h not only have a lower 30-day mortality, but have a reduced myocardial infarct size and consequently a better preserved left ventricular function. As ventricular function is a main determinant of long-term survival in patients with coronary artery disease, very early treatment probably conveys additional benefits. In this study, the number of patients treated very early is too small to allow analysis.

Total ischaemic time and its consequences

Total ischaemic time is composed of four parts: (1) patient delay, (2) medical response delay, (3) delay in initiation of therapy, (4) delay before therapy becomes effective. Patient delay is a major concern, as out-of-hospital mortality is still considerable, and many patients die before medical attention is sought[33]. With increasing public awareness, this may be reduced. The medical response delay consists of the time needed for the ambulance service to reach the patient, transportation and initial diagnosis. Out-of-hospital diagnosis can result in large reductions in ischaemic time[33,34]. The delay in initiation of therapy is important, particularly

Table 7 Thirty day and 6 month mortality according to thrombolytic agent

	rtPA (n=978)			Streptokinase (n=355)	
	30 days	6 months		30 days	6 months
Early (<2 h) (n=325)	5·5%	6·2%	(n=99)	3·0%	3·0%
Intermediate (2–4 h) (n=414)	5·6%	6·8%	(n=109)	9·2%	9·2%
Late (>4 h) (n=218)	12·4%	14·7%	(n=97)	11·3%	14·4%
Test for trend *P*-value	0·006	0·001		0·04	0·007

No significant interaction between the streptokinase and rtPA groups on these trends was seen for either the 30-day ($P=0·90$) or the 6 months ($P=0·86$) outcomes.

for patients treated by primary angioplasty[9,10], probably as this delay reflects quality of care. Organizational skills, logistical expertise and optimal use of all aspects of care are likely to have major effects on outcome. Finally, after initiation of therapy, it takes some time before therapy becomes effective in restoring flow in the epicardial coronary artery and subsequently into the ischaemic and infarcted myocardial territory. In particular after the initiation of thrombolytic therapy, 90 min later almost half of patients will not (yet) have a patent artery with TIMI 3 flow[20].

Limitations

Our study shows that time, as defined in this study, is less important for the outcome of the patient than patient characteristics such as age and haemodynamic variables. However, some of the important consequences of time, such as early out-of-hospital death, are not represented in our data. Compared to the very large thrombolysis trials[1], the number of patients treated with primary angioplasty is still limited, and we may therefore be underpowered to detect a time effect. Angiographic data, or indirect measures of myocardial reperfusion are not available. There is variability in the outcomes after angioplasty in these trials[13–23] which has been shown in other studies of patients undergoing percutaneous coronary interventions[35–38].

Conclusions

1. Major adverse cardiac event rates are lower after angioplasty compared to thrombolysis, irrespective of time to presentation.
2. With increasing time to presentation, major adverse cardiac event rates increase significantly after thrombolysis and appear to remain relatively stable after angioplasty.
3. Time to presentation is related to clinical variables that have a strong influence on outcome: age, gender, systolic blood pressure, heart rate and diabetes.
4. Multivariate analysis shows that in angioplasty patients age and systolic blood pressure are determinants of 30-day mortality. Age, systolic blood pressure, infarct location and previous myocardial infarction are determinants of 30-day mortality in thrombolysis patients.

The consequences of a longer presentation delay likely reflect differences in baseline characteristics, that have a strong influence on outcome.

References

[1] Fibrinolytic Therapy Trialists' (FTT) collaborative group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomized trials of more than 1000 patients. Lancet 1994; 343: 311–22.
[2] Weaver WD, Simes RJ, Betriu A *et al*., for the Primary Coronary Angioplasty versus Thrombolysis Collaboration Group. Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: a quantitative overview. JAMA 1997; 278: 2093–8.
[3] Boersma E, Maas ACP, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. Lancet 1996; 348: 771–5.
[4] O'Neill WW, de Boer MJ, Gibbons RJ *et al*. Lessons from the pooled outcome of the PAMI, Zwolle and Mayo Clinic randomized trials of primary angioplasty versus thrombolytic therapy of acute myocardial infarction. J Invas Cardiol 1998; 10: 4A–10A.
[5] Steg PG, Laperche T, Golmard JL *et al*., for the PERM study group. Efficacy of streptokinase, but not issue-type plasminogen activator, in achieving 90-minute patency after thrombolysis for acute myocardial infarction decreases with time to treatment. J Am Coll Cardiol 1998; 31: 776–9.
[6] Zeymer U, Tebbe U, von Essen R, Haarmann W, Neuhaus KL, for the ALKK-study group. Influence of time to treatment on early infarct-related artery patency after different thrombolytic regimens. Am Heart J 1999; 137: 34–8.
[7] Brodie BR, Stuckey TD, Wall TC *et al*. Importance of time to reperfusion for 30-day and late survival and recovery of left ventricular function after primary angioplasty for acute myocardial infarction. J Am Coll Cardiol 1998; 32: 1312–9.
[8] van't Hof AWJ, Liem AL, Suryapranata H, Hoorntje JCA, de Boer MJ, Zijlstra F. Clinical presentation and outcome of patients with early, intermediate and late reperfusion therapy by primary coronary angioplasty for acute myocardial infarction. Eur Heart J 1998; 19: 118–23.
[9] Cannon CP, Gibson CM, Lambrew CT *et al*. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. JAMA 2000; 283: 2941–7.

[10] Berger PB, Ellis SG, Holmes DR Jr *et al*. Relationship between delay in performing direct coronary angioplasty and early clinical outcome in patients with acute myocardial infarction: results from the global use of strategies to open occluded arteries in acute coronary syndromes (GUSTO-IIb) trial. Circulation 1999; 100: 14–20.
[11] Weaver WD. Time to thrombolytic treatment: factors affecting delay and their influence on outcome. J Am Coll Cardiol 1995; 25 (Suppl): 3S–9S.
[12] Lee KL, Woodlief LH, Topol EJ *et al*., for the GUSTO-1 investigators. Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction. Results from an international trial of 41 021 patients. Circulation 1995; 1659–68.
[13] Zijlstra F, de Boer MJ, Hoorntje JCA *et al*. A comparison of immediate angioplasty with intravenous streptokinase in acute myocardial infarction. N Engl J Med 1993; 328: 680–4.
[14] Ribeiro EE, Silva LA, Carneiro R *et al*. Randomized trial of direct coronary angioplasty versus intravenous streptokinase in acute myocardial infarction. J Am Coll Cardiol 1993; 22: 376–80.
[15] Grinfeld L, Berrocal D, Belardi J *et al*. Fibrinolytics versus primary angioplasty in acute myocardial infarction (FAP) (Abstr). J Am Coll Cardiol 1996; 27 (Suppl): A-222.
[16] Zijlstra F, Beukema WP, van't Hof AWJ *et al*. Randomized comparison of primary angioplasty with thrombolytic therapy in low risk patients with acute myocardial infarction. J Am Coll Cardiol 1997; 29: 908–12.
[17] Garcia E, Elizaga J, Perez-Castellano N *et al*. Primary angioplasty versus systemic thrombolysis in anterior myocardial infarction. J Am Coll Cardiol 1999; 33: 605–11.
[18] Grines CL, Browne KF, Marco JL *et al*. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1993; 328: 673–9.
[19] Gibbons RJ, Holmes DR, Reeder GS, Bayley KR, Hopfenspirger MR, Gersh BJ. Immediate angioplasty compared with the administration of a thrombolytic agent followed by conservative treatment for myocardial infarction. N Engl J Med 1993; 328: 685–91.
[20] The Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes. GUSTO IIb Angioplasty Substudy Investigators. A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. N Engl J Med 1997; 336: 1621–8.
[21] Akhras F, Ousa AA, Swann G *et al*. Primary coronary angioplasty or intravenous thrombolysis for patients with acute myocardial infarction? Acute and late follow-up results in a new cardiac unit (Abstr). J Am Coll Cardiol 1997; 29 (Suppl): A-235–A-236.
[22] Ribichini F, Steffenino G, Dellavalle A *et al*. Comparison of thrombolytic therapy and primary coronary angioplasty with liberal stenting for inferior myocardial infarction with precordial ST-segment depression. Immediate and long-term results of a randomized study. J Am Coll Cardiol 1998; 32: 1687–94.
[23] DeWood MA. Direct PTCA versus intravenous t-PA in acute myocardial infarction: results from a prospective randomized trial. In: Proceedings from the Thrombolysis and Interventional Therapy in Acute Myocardial Infarction Symposium VI. Washington, DC: George Washington University, 1990: 28–9.
[24] Wald A. Tests of statistical hypotheses concerning several parameters when the number of observations is large. Trans Am Math Soc 1943; 54: 426–82.
[25] Flameng W, Lesaffre E, Vanhaecke J. Determinants of infarct size in non-human primates. Bas Res Cardiol 1990; 85: 392–403.
[26] Reimer KA, Vander Heide RS, Richard VJ. Reperfusion in acute myocardial infarction: effect of timing and modulating factors in experimental models. Am J Cardiol 1993; 72: 13G–21G.
[27] Dorado DG, Théroux P, Elizaga J *et al*. Myocardial infarction in the pig heart model: infarct size and duration of coronary occlusion. Cardiovasc Res 1987; 21: 537–44.
[28] Liem AL, van't Hof AWJ, Hoorntje JCA, de Boer MJ, Suryapranata H, Zijlstra F. Influence of treatment delay on infarct size and clinical outcome in patients with acute myocardial infarction treated with primary angioplasty. J Am Coll Cardiol 1998; 32: 629–33.
[29] Milavetz JJ, Giebel DW, Christian TF, Schwartz RS, Holmes DR, Gibbons RJ. Time to therapy and salvage in myocardial infarction. J Am Coll Cardiol 1998; 31: 1246–51.
[30] Chareonthaitawee P, Gibbons RJ, Roberts RS, Christian TF, Burns R, Yusuf S, for the CORE investigators. The impact of time to thrombolytic treatment on outcome in patients with acute myocardial infarction. Heart 2000; 84: 142–8.
[31] The GUSTO investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993; 329: 673–82.
[32] Newby LK, Rutsch WR, Califf RM *et al*., for the GUSTO-1 investigators. Time from symptom onset to treatment and outcomes after thrombolytic therapy. J Am Coll Cardiol 1996; 27: 1646–55.
[33] The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. Acute myocardial infarction: pre-hospital and in-hospital management. Eur Heart J 1996; 17: 43–63.
[34] Zijlstra F. Long-term benefit of primary angioplasty compared to thrombolytic therapy for acute myocardial infarction. Eur Heart J 2000; 21: 1487–9.
[35] Kimmel SE, Berlin JA, Laskey WK. The relationship between coronary angioplasty procedure volume and major complications. JAMA 1996; 274: 1137–42.
[36] Christian TF, O'Keefe JH, DeWood MA *et al*. Intercenter variability in outcome for patients treated with direct coronary angioplasty during acute myocardial infarction. Am Heart J 1998; 135: 310–7.
[37] Caputo RP, Ho KKL, Stoler RC *et al*. Effect of continuous quality improvement analysis on the delivery of primary percutaneous transluminal coronary angioplasty for acute myocardial infarction. Am J Cardiol 1997; 79: 1159–64.
[38] Zijlstra F, Hoorntje JCA, de Boer MJ *et al*. Long-term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1999; 341: 1413–9.